



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 8/17/2016

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

## Indinavir (IDV, Crixivan) (Last updated February 12, 2014; last reviewed March 1, 2016)

For additional information see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

### Formulations

**Capsules:** 100 mg, 200 mg, and 400 mg

### Dosing Recommendations

#### Neonate and Infant Dose:

- Not approved for use in neonates/infants.
- Should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus).

#### Pediatric Dose:

- Not approved for use in children.
- A range of indinavir doses (234–500 mg/m<sup>2</sup> body surface area) boosted with low-dose ritonavir has been studied in children (see text below).

#### Adolescent and Adult Dose:

- 800 mg indinavir plus 100 or 200 mg ritonavir every 12 hours

### Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal intolerance, nausea
- Hepatitis
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

### Special Instructions

- When given in combination with ritonavir, meal restrictions are not necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis ( $\geq 48$  oz of fluid daily in adult patients).
- If co-administered with didanosine, give indinavir and didanosine  $\geq 1$  hour apart on an empty stomach.
- Indinavir capsules are sensitive to moisture; store at room temperature (59–86° F) in original container with desiccant.

### Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate
- Dosing in patients with hepatic impairment: Decreased dosage should be used in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg indinavir every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.

**Drug Interactions** (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#) and <http://www.hiv-druginteractions.org/>)

- *Metabolism:* CYP3A4 is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Avoid other drugs that cause hyperbilirubinemia, such as atazanavir.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with indinavir.

### **Major Toxicities**

- *More common:* Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritus, and rash. Nephrolithiasis/urolithiasis with indinavir crystal deposits.
- *Less common (more severe):* Fat maldistribution.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life-threatening in rare cases).
- *Pediatric specific:* The cumulative frequency of nephrolithiasis is higher in children (29%) than in adults (12.4%).

### **Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://iasusa.org/sites/default/files/tam/october\\_november\\_2015.pdf#page=10](http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

### **Pediatric Use**

#### *Approval*

Indinavir has not been approved by the Food and Drug Administration for use in the pediatric population. Although indinavir was one of the first protease inhibitors to be studied in children, its use in pediatrics has never been common and is currently very rare.<sup>1</sup>

#### *Dosing*

Both unboosted and ritonavir-boosted indinavir have been studied in HIV-infected children. Data in children indicate that an unboosted indinavir dose of 500 to 600 mg/m<sup>2</sup> body surface area given every 8 hours results in peak blood concentrations and area under the curve slightly higher than those in adults but considerably lower trough concentrations. A significant proportion of children have trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults.<sup>2-5</sup> Studies in small groups of children of a range of indinavir/ritonavir doses have shown that indinavir 500 mg/m<sup>2</sup> body surface area plus ritonavir 100 mg/m<sup>2</sup> body surface area twice daily is probably too high,<sup>6</sup> that indinavir 234 to 250 mg/m<sup>2</sup> body surface area plus low-dose ritonavir twice daily is too low,<sup>7,8</sup> and that indinavir 400 mg/m<sup>2</sup> body surface area plus ritonavir 100 to 125 mg/m<sup>2</sup> body surface area twice daily results in exposures approximating those seen with 800 mg indinavir/100 mg ritonavir twice daily in adults, albeit with considerable inter-individual variability and high rates of toxicity.<sup>8-10</sup>

#### *Toxicity*

The cumulative frequency of nephrolithiasis is substantially higher in children (29%) than in adults (12.4%, range across clinical trials 4.7% to 34.4%).<sup>11</sup> This is likely due to the difficulty in maintaining adequate hydration in children. Finally, a large analysis of more than 2,000 HIV-infected children from PACTG 219

demonstrated a hazard ratio of 1.7 for risk of renal dysfunction in children receiving combination antiretroviral therapy with indinavir.<sup>12</sup>

## References

1. Van Dyke RB, Patel K, Siberry GK, et al. Antiretroviral treatment of US children with perinatally acquired HIV infection: temporal changes in therapy between 1991 and 2009 and predictors of immunologic and virologic outcomes. *J Acquir Immune Defic Syndr*. 2011;57(2):165-173. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21407086>.
2. Burger DM, van Rossum AM, Hugen PW, et al. Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother*. 2001;45(3):701-705. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11181346>.
3. Fletcher CV, Brundage RC, Rimmel RP, et al. Pharmacologic characteristics of indinavir, didanosine, and stavudine in human immunodeficiency virus-infected children receiving combination therapy. *Antimicrob Agents Chemother*. 2000;44(4):1029-1034. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10722507>.
4. Gatti G, Vigano A, Sala N, et al. Indinavir pharmacokinetics and pharmacodynamics in children with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. 2000;44(3):752-755. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10681350>.
5. Mueller BU, Sleasman J, Nelson RP, Jr., et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics*. 1998;102(1 Pt 1):101-109. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9651421>.
6. van Rossum AM, Dieleman JP, Fraaij PL, et al. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. *Pediatrics*. 2002;110(2 Pt 1):e19. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12165618>.
7. Plipat N, Cressey TR, Vanprapar N, Chokephaibulkit K. Efficacy and plasma concentrations of indinavir when boosted with ritonavir in human immunodeficiency virus-infected Thai children. *Pediatr Infect Dis J*. 2007;26(1):86-88. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17195716>.
8. Curras V, Hocht C, Mangano A, et al. Pharmacokinetic study of the variability of indinavir drug levels when boosted with ritonavir in HIV-infected children. *Pharmacology*. 2009;83(1):59-66. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19052483>.
9. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of indinavir combined with low-dose ritonavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother*. 2004;48(5):1904-1907. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15105157>.
10. Fraaij PL, Bergshoeff AS, van Rossum AM, Hartwig NG, Burger DM, de Groot R. Changes in indinavir exposure over time: a case study in six HIV-1-infected children. *J Antimicrob Chemother*. 2003;52(4):727-730. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12917234>.
11. Crixivan [package insert]. Food and Drug Administration. 2010. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020685s0731b1.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020685s0731b1.pdf). Accessed December 18, 2015.
12. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J*. 2009;28(7):619-625. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19561425>.